EXHIBIT A

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Reviews • POST SCREEN

New therapeutics that treat rheumatoid arthritis by blocking T-cell activation

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Despite the recent introduction of several new biological products, there remains a significant unmet medical need in rheumatoid arthritis. A focus on the aberrant activation of autoimmune T cells, which is integral to pathogenesis, is a promising approach involved in several of these new therapies. In choosing a molecular target for the modification of T-cell function, it is argued in this article, that within co-stimulatory pathways, CD80 could have a more compelling rationale than CD86. Data are presented showing that CD80-mediated T-cell activation can be inhibited using a small-molecule antagonist, which offers the potential to prevent the inflammatory process leading to joint destruction.

Rheumatoid arthritis (RA) is a common disease in which, despite the recent introduction of several powerful disease-modifying anti-rheumatic drugs (DMARDs), there remains a significant unmet medical need. DMARDs reduce joint inflammation and pain and might prevent joint destruction and deformity; however, clinical responses are incomplete, with only ~60% of patients achieving an ACR20 response (American College of Rheumatology defined responses; http://www.rheumatology.org) (Table 1). In all these studies, the proportion of patients achieving an ACR70 response (70% reduction in symptoms) was very much lower still. The need for further advances and alternative therapies is therefore clear. In this article, a new approach to the treatment of RA is proposed, through downregulation of the early stages of the T-cell response, which is clearly involved in pathogenesis [1].

Rheumatoid arthritis: a major disease where a large unmet medical need exists

Rheumatoid arthritis (RA) is a chronic systemic disease primarily affecting the joints and is marked by inflammatory changes in the synovium and adjacent structures. Long-term prognosis is poor, with 80% of affected patients being disabled after 20 years. In the USA, medical costs are estimated to be on average US$5,919 per case per year. RA affects 0.8–1.0% of adults and is three times more prevalent in woman than men. This translates into 2.1 million cases in the USA, of which 600,000 are men and 1.5 million are women. The current worldwide market for RA drugs exceeds US$14 billion annually.

Therapy for RA has evolved as the understanding of the disease has progressed. The finding that joint damage occurs early in the disease course has led to treatment paradigms that emphasize early treatment with cellular proliferation inhibitors, such as methotrexate. Moreover, advances in the molecular understanding of immunology and inflammation have led to the development of protein therapeutics [1], such as those listed in Table 1. However, because many patients do not achieve an adequate response to these agents, there remains a need for new therapeutic approaches with new mechanisms of action.

Breakdown of immune tolerance in rheumatoid arthritis

Although it is not clear how RA is triggered, it is clear that a breakdown in the control of inflammation mediated by CD4+ cells is centrally important [1]. The result is an aberrant inflammatory response against the healthy tissues, which are, of course, not normally attacked. The inflammation is associated with infiltration of immune cells, such as macrophages, which in turn present antigens to T cells, resulting in their increased activation [2]. T-cell activation results in cytokine release and a cascade of immune and inflammatory processes causing both the symptoms of disease progression and joint destruction. This has been demonstrated in animal models [3] by inducing secretion of pro-inflammatory cytokines [4]. Human leukocyte antigens (HLAs) on the surface of

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TABLE 1

ACR response rates versus placebo for recently introduced DMARDs

DMARD	ACR20 rate vs placebo (%)	Reference
Infliximab	58 vs 20	[46]
Etanercept	71 vs 27	[47]
Adalimumab	63 vs 30	[48]
Anakinra	42 vs 23	[49]
Abatacept	50 vs 20	[15]

macrophages present autoreactive antigens to T cells. Certain types of HLA, such as HLA DR4 [5], among others [6], are associated with more severe forms of RA, highlighting the importance in this disease of antigen presentation and the subsequent activation of T cells. Inhibition of T-cell activation would be predicted to reduce this cascade of events [2].

Aberrant T-cell activation triggers disease in rheumatoid arthritis

The central role of antigen-specific T cells in the pathogenic immune response in RA has been described elsewhere [7]. Antigen recognition by T cells activates a host of pathways, which lead to the production of cytokines, prostaglandins, leukotrienes and oxygen free radicals, as well as recruiting further immune cells [8]. These factors act in concert to exacerbate the response. The result of this process is full-blown disease and tissue destruction leading to the clinical manifestations of RA [1].

No current cure for rheumatoid arthritis

Before modern treatments were available, unchecked rheumatoid arthritis caused significant disability and mortality [9]. It is now accepted that early diagnosis and treatment are necessary and beneficial [10,11] and the realistic aim of disease management is to achieve complete remission, with cessation of fatigue, relief of pain, prevention of deformity and maintenance of normal function. Although long-term outcomes have been remarkably improved with these approaches, there remains no cure.

Biological disease-modifying anti-rheumatic drugs in development

The emergence onto the market of biological DMARDs, shown in Table 1, which act by blocking the pro-inflammatory cytokines human tumour necrosis factor α (TNF-α) and interleukin-1 β (IL-1β), led to the development of treatment strategies involving their early introduction into therapeutic regimens [11]. However, since the demonstration of efficacy and the launch of three anti-TNF proteins, etanercept (Enbrel®), infliximab (Remicade®) and adalimumab (Humira®), nonresponders and partial responders to TNF blockade have been found to be frequent [12]. Other investigational antibodies directed against IL-6 (tocilizumab; Actemia®) [13] and IL-15 (Humax-IL15) [14], are now in development and are looking promising (Figure 1).

More recently, agents that are designed to inhibit T-cell activation (rather than block the consequences of activation, as current biological DMARDs do) are now under investigation. Most products in this new class act by blocking T-cell receptors or their co-receptors directly and could therefore have application in rheu-

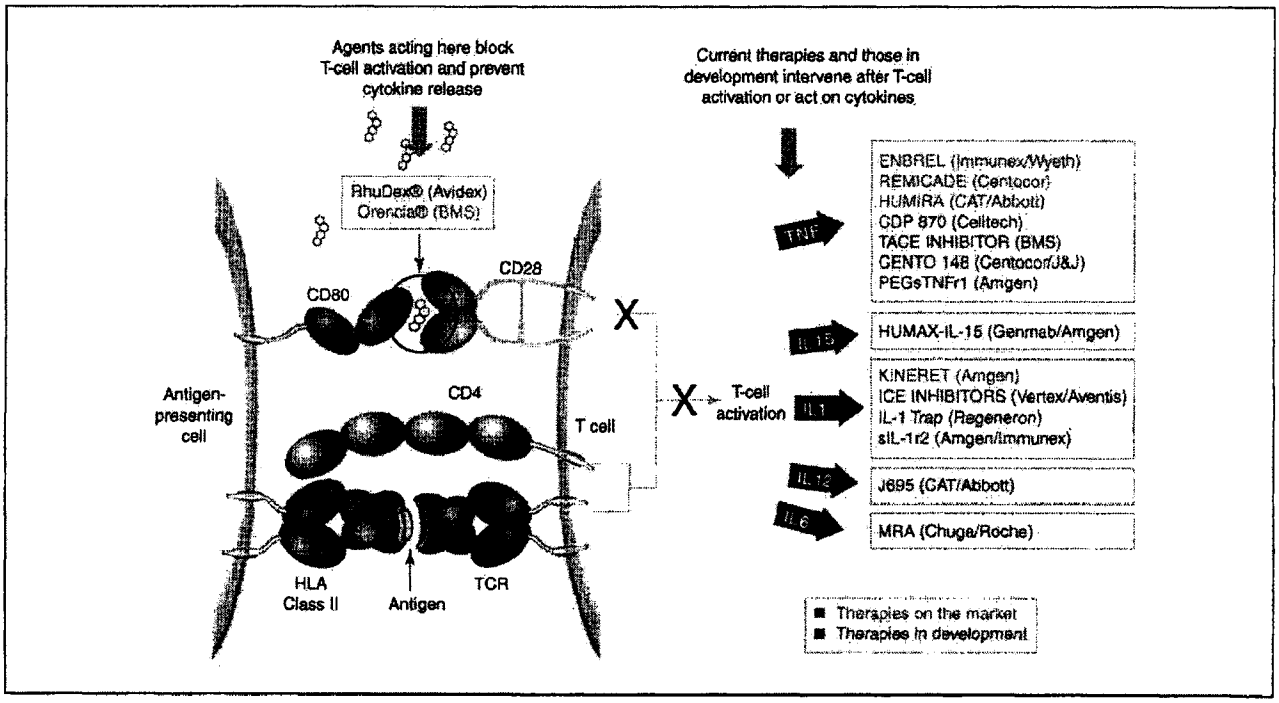

FIGURE 1

Site of action of therapeutics for rheumatoid arthritis. The products on the market, or in development, and their site of action in the pathway of T-cell activation and cytokine release. By blocking the primary T-cell activation pathways, RhuDex® and Orencia® can prevent the release of cytokines directly. Figure reproduced, with permission, from Avidex.

matoid arthritis. These include products that block the action of CD2 (Amevive® from Biogen), CD4 (Humax from Genmab, Clenoliximab from IDEC and TRX1 from TolerRx) and products that block the co-stimulatory signal interactions of CD154 with CD40 (Ruplizumab and IDEC 131 from Biogen-IDEC), of CD11a with LFA-1n (Raptiva from Xoma) and of CD86 and/or CD80 with CD28 (CTLA4-Ig-188667, also known as Abatacept, now Orencia®, from BMS, and IDEC 114 from IDEC). Of these, only the BMS and Biogen-IDEC products have been in clinical trials for the treatment of rheumatoid arthritis [15] (as opposed to other autoimmune diseases) and BMS has recently achieved a marketing authorization for RA for Orencia® (http://www.orencia.com).

Clinical development

The market for new drugs for rheumatoid arthritis is highly competitive, with considerable research activity and new entrants. Market entry, whether into clinical research or commercialisation, is driven by novelty and perceptions of benefit against risk, among other important factors.

Clinical trial methods in RA are well-established and standardized. Definitive proof of anti-inflammatory effect can be obtained with a three month, or longer, study using the ACR-defined responses, compared with placebo – as in the studies referenced in Table 1. Proof of disease-modifying effect is similarly well defined, but requires a longer duration of 12 months or more [16]. Current standards are set by the various anti-TNF therapies and reinforced by recent data on abatacept [15] and rituximab [17] showing very similar rates of efficacy.

Clinical trials of these agents show that, although a proportion of clinical responses occur within four weeks of the start of treatment, large components of the ACR scoring system are subjective and there is also a substantial placebo response (~20%). The difference between treatment and placebo in ACR20 responses tends to increase in most trials to a maximum after about three months of treatment. However, a large change in the acute-phase protein C-reactive protein (CRP), a standard component of the ACR response scoring system that is not subjective, occurs within one week or less of the start of treatment without any significant accompanying placebo response [18]. This provides a possible basis for a short term proof-of-principle assessment of effect for agents inhibiting T-cell activation. The magnitude of treatment effect on CRP and the small placebo effect allow small patient numbers to be used. This gives rheumatoid arthritis some attractive features as a target for an early-phase pilot study in comparison to other autoimmune diseases.

T cell co-stimulation and chronic inflammatory autoimmune disease

T-cell activation plays a central role in driving normal and pathogenic immune responses [7]. This process, which is initiated by the recognition of the antigen major histocompatibility complex by the T-cell receptor (TCR), is regulated by additional accessory T-cell surface receptors or co-stimulatory molecules that interact with specific ligands on antigen-presenting cells [19]. Co-stimulation is required to complement and amplify early TCR signalling by generating unique intercellular signalling events [20] and/or the clustering of membrane intercellular kinase-rich microdomains at the site of TCR engagement [20]. Current concepts predict that in the absence of co-stimulation, T-cell activation will be impaired or aborted, which might lead to a state of antigen-specific unresponsiveness or anergy [21,22]. The co-stimulatory molecules B7-1 (CD80) and B7-2 (CD86) provide one dominant T-cell co-stimulatory pathway. B7-1 and B7-2 belong to the immunoglobulin (Ig) superfamily and share ~25% amino acid identity in their Ig variable (IgV) and Ig constant (IgC) extracellular regions. Interaction of CD28 on T cells with either B7-1 or B7-2 augments T-cell activation [19,23] and promotes T-cell survival [24]. By contrast, recent data suggest that binding of B7-1 or B7-2 with cytotoxic T lymphocyte antigen 4 (CTLA-4), a homologue of CD28, might inhibit the T cell response by delivering a putative negative signal [25,26].

T cells can distinguish self from non-self antigens – called 'peptide antigens' – through the TCR. These peptide antigens are found on the surface of cells only combined with an HLA molecule. The role of HLA is to present the antigen on the surface of an antigen-presenting cell, which allows the T cell, via its TCR, to recognize and bind the peptide antigens. T cells binding 'self' antigens on antigen-presenting cells are not normally activated. However, in RA, this self–non-self discrimination breaks down and T cells become aberrantly activated to the self antigens [1–3,7]. Blocking the interaction between a TCR and the peptide-HLA antigen is difficult but can be done with soluble recombinant human monoclonal TCR proteins [27].

The discovery that CTLA-4 is not delivering a positive co-stimulatory signal to TCRs like CD28, as originally thought, but instead serves to downregulate T-cell responses, raises the concern that blocking B7–CTLA-4 interaction might have unpredictable effects and perhaps even exacerbate certain immune responses [25]. However, preclinical and clinical studies with CTLA4–Ig do not support this possibility [28,29]. Rather, the data provide convincing evidence that CTLA4–Ig exerts immunosuppressive activity. This might be because blockage of the B7–CTLA-4 interaction is more difficult to achieve than blockage of the B7–CD28 interaction – CTLA-4 is bivalent whereas CD28 is monovalent [30]. However, the dynamics of the system are also quite subtle. For example, CD28 is expressed well on unprimed and memory T cells before activation, whereas CTLA-4 is upregulated after activation [31].

Rationale for selection of CD80 (over CD86) as a target

There are numerous studies that examine the role of the B7 pathway in disease models and in humans – some are listed below. These show that blocking the B7 signal can significantly reduce the severity of disease. However, of the two B7 proteins, there is better rationale to choose CD80 as a target rather than CD86 for the following reasons.

Selective deletion of CD80 significantly diminishes T-cell responses. CD80 gene-deficient mice revealed a 70% decrease in the allogeneic T-cell-mediated response. This result indicates that CD86 is unable to compensate for loss of CD80, at least in a mixed lymphocyte reaction (MLR) assay driven by MHC disparity [26]. Because it is generally accepted that T cells play an essential role in the initiation and progression of autoimmune disease, the ability to block up to 70% of T-cell responses in MLR assays supports a key role for CD80 in T-cell activation.

CD80 is dominant in established disease. CD80 expression is low on unstimulated professional antigen-presenting cells

but becomes a dominant co-stimulatory receptor in established immune responses [32,33]. By contrast, CD86 does not appear to show such pronounced upregulation in disease. This suggests that CD80 could be the preferred target in chronic disease [34].

CD80 is the high affinity interaction. CD80 has a higher affinity for CD28 (and CTLA-4) than does CD86, so CD80 is potentially a more potent co-stimulatory receptor than CD86 and therefore a more attractive target [30].

In addition, examining the role of the two co-receptors in other disease models, such as experimental allergic encephalitis, provides additional support for the rationale [32,35–37]. Of course, care must be taken in extrapolating from disease models into man and attempting to correlate the relative roles of the two molecules across the different disease models.

T-cell activation requires a first and a second signal

Recognition of the peptide–HLA complex by the TCR (often called the first signal) is not enough to propagate full T-cell activation; indeed, the signal must first be amplified. For the amplification of this signal to occur, a second recognition event must take place between another set of cellular receptors (namely co-stimulatory receptors).

APCs express several co-stimulatory ligands on the cell surface. CD80 and CD86 are two such ligands, both of which are capable of engaging either the CD28 or CTLA-4 co-stimulatory receptors on T cells. When T cells receive a signal through CD28, cellular activation and proliferation ensues, but when CTLA-4 is engaged, the T-cell response is attenuated [25]. This balance of positive and negative signalling provides the basis of immune regulation. In a normal host, the immune system is nonresponsive, or tolerant to self. However, in autoimmune diseases, such as rheumatoid arthritis, control mechanisms are breached and an inappropriate response to self-components is initiated.

Numerous studies have shown that dual blockade of CD80 and CD86 can significantly reduce the severity of autoimmune disease and this suggests that these co-stimulatory ligands might be useful targets in treatment of autoimmune disease [38,39]. Based on their patterns of expression during the immune response, it appears that CD86 is the primary co-stimulatory ligand involved in early T-cell activation, whereas CD80 is the functionally predominant co-stimulatory ligand in established responses [33,34]. In chronic autoimmune diseases associated with on-going responses, CD80-specific inhibitors would be the preferred agents, leaving primary T-cell responses to recently encountered foreign pathogens relatively unaffected. This suggests that there might be advantages in CD80 monotherapy for the treatment of established chronic autoimmune disease.

There is a growing body of evidence to suggest that selective blockade of CD80 might have significant therapeutic benefit in the treatment of autoimmune disease [34,38–40]. Rheumatoid synovitis is characterised by a marked infiltration of mononuclear cells and the presence of a highly differentiated population of dendritic cells in the synovial tissue and fluid of affected joints [41]. The presence of these cells correlates with clinically active RA, and the expression of CD80 and CD86 implicates T-cell co-stimulation in active disease [33,42]. Activated T cells in the synovial fluid of RA patients express CD80 and it is thought that these cells can also function as antigen-presenting cells [33].

To date, the most compelling data have been generated in nonclinical models of rheumatoid arthritis. *In vitro* studies using antibodies have shown that the production of pro-inflammatory cytokines (IL-1β and IL-6) by human synovial cells can be inhibited by anti-CD80 antibodies [34]. *In vivo* studies using anti-CD80 antibodies in combination with anti-CD86 antibodies or CTLA–4Ig treatment have shown reduced disease incidence and clinical score in murine collagen-induced arthritis [39,40]. There is only limited work examining CD80 monotherapy in animal models of RA. However, the *in vivo* antibody studies have recently been extended using the same murine collagen-induced arthritis model, treated with an anti-CD80 peptide [40]. This peptide was specific for CD80 and did not inhibit the binding of CD86 with its receptors on the APC, demonstrating the utility of CD80 treatment [40].

What compounds targeting CD80 are in development?

Recent trials with CTLA4Ig (Orencia®, BMS) [15] have shown that dual blockade of CD80 and CD86 is effective in RA and therefore validates the CD80 and CD86 targets in autoimmune disease. Although CTLA4Ig has been found to be safe as monotherapy, long-term co-administration with anti-TNF therapies is associated with an increased risk of serious infection [43]. This implies the possible advantages of selective inhibition of the immune response and the shorter half life of an orally administered NCE as opposed to an injectable antibody.

RhuDex® is an orally bioavailable small molecule antagonist of CD80 [44]. Given that CD80 is implicated in the development of autoimmune diseases like RA, RhuDex® might be useful in the treatment of such diseases. RhuDex® binds CD80, preventing recognition of CD28, and therefore blocks the second signal. If T-cell activation is prevented, no cytokines are released, preventing the sequence of events leading to joint destruction.

Based on their patterns of expression during the immune response, CD86 seems to be the primary co-stimulatory ligand involved in early T-cell activation, whereas CD80 is more dominantly expressed in chronic disease. Therefore, CD80-specific inhibitors might be the preferred agents in chronic autoimmune diseases, and might leave beneficial primary T-cell responses to recently encountered foreign pathogens relatively unaffected, but this is yet to be proven.

Orencia® is proving to be an excellent clinical candidate in RA. However, Rhudex®, which specifically blocks the CD80 receptor, could offer advantages over biologicals for RA for several reasons. It inhibits the high avidity receptor, CD80 and no others, and is administered orally, rather than parenterally. Moreover, low molecular weight organic drugs are generally not immunogenic and, of course, such drugs generally have a lower cost of goods [45].

Conclusion

CD80 represents a logical choice of target for a small-molecule programme. There remains a clear unmet medical need for a new oral therapeutic for RA, which:

- Intervenes early in the disease process.
- Treats the causes and not the symptoms of disease.
- Has minimal bystander effects and leaves the immune system functional.

Avidex has shown that CD80 is a 'drugable' target by developing potent, drug-like small molecules. Rhudex® could potentially be the first-in-class as a novel, but orally available, blocker of T-cell activation – an ideal product profile for chronic inflammatory diseases. By virtue of its novel mode of action, Rhudex® is well positioned to combine high selectivity with high potency. It should be applicable across a wide range of inflammatory and autoimmune disease.

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